Anterior thalamic nuclei lesions have a greater impact than mammillothalamic tract lesions on the extended hippocampal system: A reply

Dear Editor,

Perry et al. recently carried out a replication of anterior thalamic nuclei (ATN) and mammillothalamic tract (MTT) lesion studies, looking at the effects of these lesions on watermaze and radial-arm maze tasks. Consistent with previous findings, they found MTT lesions impaired working memory tasks in both the water-maze (Santin et al., 1999; Vann, 2013; Vann and Aggleton, 2003) and radial-arm maze (Nelson and Vann, 2014; Vann, 2013; Vann and Aggleton, 2003). In contrast, rats with MTT lesions were unimpaired on a reference memory task in the water-maze, again consistent with studies showing mammillary body lesions have little or no effect on this task (Santin et al., 1999; Sutherland and Rodriguez, 1989). The authors found more pronounced impairments following ATN lesions, which is again consistent with previous studies that have directly compared ATN and mammillary body lesions (Aggleton et al., 1991; Aggleton et al., 1995; Gaffan et al., 2001) (see also Sutherland and Rodriguez (1989) who tested rats with mammillary body and ATN on the same water-maze task). Those studies found ATN lesions to be more disruptive than mammillary body lesions on standard tasks, including T-maze alternation, but there was greater similarity across the lesion groups when task demands increased or non-spatial cues were removed.

Perry et al.'s behavioural findings are therefore entirely as expected given our current knowledge. However, the authors claim to be testing a model that predicts equivalent impairments following lesions of the MTT and ATN. Furthermore, they erroneously imply that this is a position that we have advanced. For example, in the abstract it is written, "**it is assumed that their (the MTT and ATN) influence on memory is functionally equivalent**". In the Introduction it is written, "**New experimental evidence suggests a more prominent influence of the MTT and a greater influence of the MB's brainstem connections on the integrity of the extended hippocampal system than was previously recognised (Dillingham et al., 2015; Vann and Nelson, 2015). The latter perspective suggests that equivalent deficits after MTT and ATN injury would be common-place rather than the exception";** in the Discussion they write, "**recent animal work, however, has shown that brainstem structures influence the memory system upstream via their impact on the MB, which suggests that damage to the MTT afferents to the ATN would produce comparable memory impairments to that found after ATN lesions (Vann, 2013; Dillingham et al., 2015; Vann and Nelson, 2015)**." In setting up the study in this manner the authors have simply created a straw-man argument. This is not a viewpoint we hold and this is not what is written in the papers that are cited; such claims would disregard both anatomical and functional data (e.g., Jankowski et al., 2013). Furthermore, while the tegmental inputs have been shown to be important, it does not follow that MTT and ATN lesion effects would be comparable, i.e., highlighting a role for the tegmental inputs does not automatically reduce the previously identified contributions of other thalamic connections. Given ATN lesions

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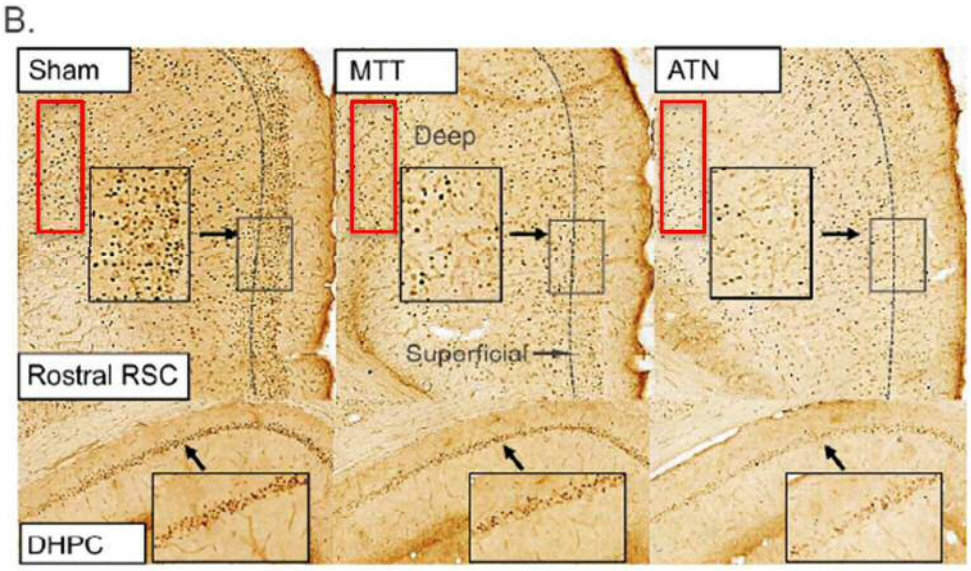
result in retrosplenial/hippocampal deafferentation and the ATN have a number of efferents and afferents that have been shown to support memory, it is self-evident that ATN lesions should produce greater impairments. We would never say otherwise given much of the data to the contrary comes from our own laboratories. In the Dillingham et al. (2015) paper we devote an entire section to the finding that ATN lesions are typically more disruptive than MTT lesions and possible reasons for this dissociation (p.113-114). In the Vann and Nelson (2015) paper we state, "a further implication is that anterior thalamic lesion effects are to some extent driven by the loss of their inputs from mammillary body lesions" (p.170). The 'to some extent' makes it clear that we are not espousing that the ATN function can be explained entirely by their mammillary body inputs.

An additional issue is that the authors do not give an accurate representation of the findings from the geometric task in the watermaze. In the Introduction they write, **"For example, MTT lesions in rats were reported to show weak and transient reference memory impairments in the standard water-maze in one report and did not impair geometric learning in a water-maze in another study (Winter et al., 2011; Vann, 2013). By contrast, ATN lesions produce profound deficits on both tasks (Warburton et al., 1999; Wolff et al., 2008; Aggleton et al., 2009; Dumont et al., 2014)"** and again in the Discussion, **"differences between the spatial memory effects of ATN lesions and MTT lesions have been reported using other tasks. Rats with MTT lesions are able to discriminate the fixed location in a geometric learning task at the same rate as controls whereas rats with ATN lesions remain at chance levels (Aggleton et al, 2009; Vann, 2013; Dumont et al., 2014)."** This is misleading. In terms of the geometric task, MTT lesions that *spare the lateral mammillary projections* did not affect task performance (Vann, 2013). In contrast, lateral mammillary body lesions significantly impaired performance on the geometric task (Vann, 2011). Fornix lesions do not affect performance of this geometric task (Aggleton et al., 2009). Therefore, the most parsimonious argument is that this task is particularly sensitive to lesions within the head direction system. So our point was that this is not a distinction between the ATN and MTT/mammillary bodies but a distinction between head direction and non-head direction regions (Aggleton et al., 2009; Vann, 2011; Vann, 2013).

Finally, the authors assessed Zif268 expression in their lesion groups. However, they do not make it clear that their Zif268 results for the MTT lesion group differ from a previous study (Frizzati et al., 2016). The authors make a point that their MTT lesions do not affect Zif268 in deep retrosplenial layers or reduce Zif268 in dysgranular cortex. However, we found decreases in superficial and deep layers in both Rgb and dysgranular retrosplenial cortex (Frizzati et al., 2016). These differences may be due to our more stringent criteria for lesion inclusion or because we [and (Dumont et al., 2012) whose results also differed from those presented by Perry et al.] closely controlled the behavior across our experimental groups. These points aside, there does seem to be a reduction in Zif268 staining in the deep layers of the MTT group when looking at Figure 2b (see areas highlighted in red), although this apparent visual reduction does not correspond with the quantitative analyses, so perhaps this brain section is not representative.



In summary, the authors found a marked spatial impairment on two behavioural tasks following MTT lesions, consistent with previous reports. They found more widespread impairments following ATN lesions, again consistent with previous reports. There is consensus across the field that while the projections from the mammillary bodies to the anterior are important for some aspects of memory, in particular rapid allocentric encoding, other non-mammillary body projections also contribute. It must be the goal of future research to use more nuanced behavioural tasks combined with selective lesions of inputs to the anterior thalamic nuclei to determine the specific roles of these different pathways for memory.

Yours Faithfully,

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